UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/662,044	09/11/2003	Subhra Chakrabarti	078200-0305447	8318

21971 7590 02/03/2006

WILSON SONSINI GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

EXAMINER	
JOYCE, CATHERINE	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 02/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/662,044	CHAKRABARTI ET AL.	
	Examiner	Art Unit	
	Catherine M. Joyce	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-84* is/are pending in the application.

4a) Of the above claim(s) *1-52 and 84* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *53-83* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1. Claims 1-84 are pending, and claims 1-52 and 84 are withdrawn from consideration as being drawn to a nonelected invention.

2. Claims 53-83 are under examination.

3. Applicant's election without traverse of the invention of Group VIII, claims 53-83, in the reply filed on November 7, 2005 is acknowledged. Applicant's election of the species "proliferating lung cells", "colon hyperproliferating cells", "stage IV tumors", and "metastatic tumors" is also acknowledged.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 82 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 82 recites the phrase "an antibody". However, the metes and bounds of the claim cannot be determined because it is unclear what type of antibody is being claimed. For example, is the antibody related in any way to the claimed treatment, is it a targeting antibody, an antibody that is cytotoxic, amendment of the claim to clarify what is intended is required.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 53-83 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to the following inventions: (i) a method of inhibiting or preventing the proliferation of a cell that expresses AgRM4 comprising contacting the cell with an amount of an isolated human monoclonal antibody that is designated RM4 and that selectively binds AgRM4 (claims 53-61), (ii) a method of treating a hyperproliferative cell disorder, wherein at least a portion of the hyperproliferative cells express AgRM4, comprising administering to a subject an amount of the isolated human monoclonal antibody that is designated RM4 and that selectively binds to an antigen designated AgRM4, the isolated human monoclonal antibody that is designated RM2 and that selectively binds to an antigen designated AgRM2, or the antibody that is designated RM4 and the antibody that is denoted RM2 (claims 62-66); and (iii) a method treating a subject having or at risk of having a tumor comprising administering to the subject an amount of the antibody designated RM4 that selectively binds to an antigen designated AgRM4 (claims 67-82), wherein the method further comprises administering the antibody RM2 (claim 83).

It is unclear if a cell lines which produce antibodies having the exact structural and chemical identity of RM2 and RM4 are known and publicly available, or can be reproducibly isolated without undue experimentation. Clearly, without access to hybridoma cells line producing monoclonal antibodies RM2 and RM4, it would not be possible to practice the claimed invention. Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of (1) a cell line which produces the chemically and functionally distinct antibody claimed and/or (2) the claimed antibody's amino acid or

nucleic acid sequence is an unpredictable event.

Applicant's referral to the deposit of the hybridoma cell lines that produce the RM2 and RM4 antibodies in the claims and on page 2, lines 14-18, of the specification, for example, is an insufficient assurance that all required deposits have been made and all the conditions of MPEP 608.01 (p)(c) have been met.

If a deposit has been made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposits will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository is required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

In addition to the conditions under the Budapest Treaty, applicant is required to satisfy that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications. Applicant's provision of these assurances would obviate this objection/rejection.

Affidavits and declarations, such as those under 37 C.F.R. 1.131 and 37 C.F.R. 1.132, filed during prosecution of the parent application do not automatically become a part of this application. Where it is desired to rely on an earlier filed affidavit, the applicant should make the remarks of record in the later application and include a copy of the original affidavit filed in the parent application

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing

the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of the deposit.

If the original deposit is made after the effective filing date of an application for patent, the applicant should promptly submit a verified statement from a person in a position to corroborate the fact, and should state, that the biological material which is deposited is a biological material specifically identified in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which the case the statement need not be verified. See MPEP 1.804(b).

7. Claims 53-83 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for (i) a method of inhibiting or preventing the proliferation of a cell that expresses AgRM4 comprising contacting the cell with an amount of an isolated human monoclonal antibody that is designated RM4 and that selectively binds an antibody designated RM4 wherein the cells are colon cancer cells or lung cancer cells, (ii) a method of treating a hyperproliferative cell disorder, wherein at least a portion of the hyperproliferative cells express AgRM4, comprising administering to a subject an amount of the isolated human monoclonal antibody that is designated RM4 and that selectively binds to an antigen designated AgRM4, wherein the hyperproliferative disorder is lung cancer or colon cancer; and (iii) a method treating a subject having or at risk of having a tumor comprising administering to the subject an amount of the antibody designated RM4 that selectively binds to an antigen designated AgRM4, wherein the tumor is a lung tumor or a colon tumor, does not reasonably provide enablement for a (i) a method of inhibiting or preventing the proliferation of a cell that expresses AgRM4 comprising contacting the cell with an amount of an isolated human monoclonal antibody that is designated RM4 and that selectively binds an antibody designated RM4, (ii) a method of treating a hyperproliferative cell disorder, wherein at least a portion of the hyperproliferative cells express AgRM4, comprising administering to a subject an amount of the isolated human monoclonal antibody that is designated RM4 and that selectively binds to an antigen

designated AgRM4, and (iii) a method treating a subject having or at risk of having a tumor comprising administering to the subject an amount of the antibody designated RM4 that selectively binds to an antigen designated AgRM4. It is noted that claims 53-61 read on both in vitro as well as in vivo inhibition of proliferation/cancer cell treatment.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

As drawn to in vivo inhibition, the claims are drawn to (i) a method of inhibiting or preventing the proliferation of a cell that expresses AgRM4 comprising contacting the cell with an amount of an isolated human monoclonal antibody that is designated RM4 and that selectively binds an antibody designated RM4 (claims 53-61), (ii) a method of treating a hyperproliferative cell disorder, wherein at least a portion of the hyperproliferative cells express AgRM4, comprising administering to a subject an amount of the isolated human monoclonal antibody that is designated RM4 and that selectively binds to an antigen designated AgRM4, the isolated human monoclonal antibody that is designated RM2 and that selectively binds to an antigen designated

AgRM2, or the antibody that is designated RM4 and the antibody that is denoted RM2 (claims 62-66); and (iii) a method treating a subject having or at risk of having a tumor comprising administering to the subject an amount of the antibody designated RM4 that selectively binds to an antigen designated AgRM4 (claims 67-83).

The specification teaches the isolation of the human monoclonal antibody RM4 by pooling regional draining lymph nodes from patients with colon cancer, isolating lymphocytes from the lymph nodes and fusing the lymphocytes with RN15 cells to form hybridomas (page 43, lines 7-28), and assessing the RM4 antibody as reactive with breast, colon, gastric and lung cancer cell lines (page 45, Table 4). The specification also teaches that immunohistochemistry analysis indicates that the RM4 antibody is reactive with breast, colon, and lung tumor tissue, but is not reactive with normal tissues (page 46, Table 5). The specification also teaches that immunohistochemistry analysis indicates that the RM2 antibody is reactive with breast, lung, melanoma, pancreatic tumor tissue but is not reactive with normal tissues (page 41, Table 2). The specification also teaches that the RM4 antibody was effective in causing tumor regression in mice that were injected with a human colon cancer cell line Colo205 (page 47, lines 15 thru page 48, line 2 and Table 7) and that the combination of the RM4 antibody with the RM2 antibody showed synergistic activity in causing tumor regression in mice injected with a human lung cancer cell line Calu 1 (page 48 lines 13-23 and Figure 3). The specification also teaches that although the RM4 antibody was effective in causing tumor regression in mice in injected with Colo205, tumor progression rapidly commenced following cessation of treatment with the RM4 antibody (page 48, Table 7).

The teaching of the specification cannot be reasonably extrapolated to the scope of the claims for the reasons that the claims encompass (i) methods of inhibiting or preventing the proliferation of all cells that express AgRM4, including all cancer cells, (ii) methods of treating a hyperproliferative disorder, wherein at least a portion of the cells express AgRM4, wherein the hyperproliferative may be any hyperproliferative disorder

(claims 62-66), or (iii) a method of treating a subject having or at risk of having a tumor, wherein the tumor may be any tumor.

One cannot extrapolate the teaching of the specification to the scope of the claims because one cannot predict that contacting any type of cell that expresses the AgRM4 with the RM4 antibody would be effective in inhibiting or preventing the proliferation of cells. The specification provides working examples that demonstrate that the proliferation of human lung and colon cancer cell lines in mice may be inhibited by contacting the cells with the RM4 antibody (i.e. administering the RM4 antibody to the mice). However, this teaching in the specification is not sufficient to establish that the proliferation of other cell types, i.e other cancer cell types or other hyperproliferative disorder cell types, may be inhibited or prevented by contacting the cells with the RM4 antibody. It is known in the art that different cancers have different etiologies and characteristics. For example, Busken et al. (2003, Digestive Disease Week Abstracts and Itinerary Planner, abstract No:850) teaches that there is a difference in COX-2 expression with respect to intensity, homogeneity, localization and prognostic significance between adenocarcinoma of the cardia and distal esophagus, suggesting that these two cancers have different etiology and genetic constitution (last five lines of the abstract). Thus based on the teaching in the art and in the specification, i.e. given the known heterogeneity of cancer types, even with cancers in the same organ, one cannot that predict that the invention will function as claimed in the inhibition of cell types other than colon cancer or lung cancer because of known differences among cancers in antigen level of expression and localization. Thus, even if the AgRM4 antigen is expressed on cancer cells or hyperproliferating cells, other than colon or lung cancer, the specification does not provide any guidance on whether the antigen is present in sufficient concentration on other cancer cell types or hyperproliferating cell types to allow for successful therapeutic targeting of the AgRM4 antigen or inhibition of cell growth or whether the receptor may be shed, modulated or down-regulated. White et al. (2001, Ann. Rev. Med. 52:125-145) teaches that, for a successful immunotherapy, besides specificity of the antibody for the antigen, other properties of the antigen should

be considered including the following: (1) the antigen should be present on all or near all of the malignant cells to allow effective targeting and to prevent a subpopulation of antigen-negative cells from proliferating; and (2) whether the antigens are shed, modulated or internalized influences the effectiveness of the administered immunotherapy (i.e. the antibody) (p. 126, second paragraph). Additionally, antigen internalization or downregulation can cause repeat dosing to be unsuccessful due to the disappearance of the antibody target (p. 126, paragraph before last). Thus, it cannot be predicted if the AgRM4 antigen is present on a sufficient number of cancer cells or hyperproliferating cells, and in sufficient quantity, to allow for successful therapeutic targeting or inhibition of the cells. Additionally, it cannot be predicted whether the antigen sheds, or is modulated internalized, or downregulated in primary cancer cells or other hyperproliferating cells. The critical nature of antigen presentation is well understood in the art as demonstrated by the well known and successful treatment of breast cancer with the antibody therapeutic trastuzumab (Herceptin®), wherein it has been demonstrated that patients can benefit from treatment with (Herceptin®) ***if*** (emphasis added) they exhibit strong overexpression of HER-2, defined by a 3+ score in IHC (immunohistochemistry), or by a rate of > 4 gene copies per nucleus and/or a ratio HER-2 gene copies to chromosome 17 copies of >2 using FISH (fluorescent in situ hybridization), or by a rate of > 5 HER-2 gene copies per nucleus using the CISH (chromogenic in situ hybridization). In the case of a 2+ score in IHC, the search for genic amplification ***must*** (emphasis added) be positive to be able to envisage such treatment (2005, Temporary protocol of treatment: Trastuzumab (Herceptin®) in adjuvant conditions, Institut National du Cancer and Agence francaise de securite sanitaire des produits de sante, www.e-cancer.fr/medias/pttdefeng2710.pdf). Clearly, adequate expression of the antigen is critical to effective treatment.

Thus based on the teaching in the art and in the specification, i.e. given the known heterogeneity of cancer antigen presentation in the same organ, given the lack of teaching drawn to intensity of antigen presentation and the apparent critical requirement for sufficient presentation, one cannot that predict that the invention will

function as claimed in the in vivo inhibition of cell types other than colon cancer or lung cancer.

Further, with regard to claims 67-83, the claims encompass methods of treating a tumor wherein the tumor cells do not express the AgRM4 antigen. However, in the absence of the expressed antigen, it could not be predicted, nor would it be expected that the administration of the antibody AgRM4 would have any effect on the tumor.

Further, with regard to claims 53-61 which encompass methods of inhibiting or preventing the proliferation of a cell that expresses AgRM4 comprising contacting the cell with an RM4 antibody in vitro, it cannot be predicted, and one of skill in the art would not expect, that the methods would function as claimed on cells in vitro other than colon cancer cells or lung cancer cells, because it cannot be predicted that other cell types would express the AgRM4 in sufficient quantity to be inhibited by the RM4 antibody.

Thus, it would require undue experimentation to practice the invention as claimed.

8. Further, if the rejection of claims 53-61 stated above were overcome, claims 53-61 would still be rejected under 35 U.S.C. 112, first paragraph, because the specification while being enabling for a method for inhibiting the proliferation of a cell that expresses AgRM4, does not reasonably provide enablement for a method for preventing the proliferation of a cancer cell that expresses AgRM4.

One cannot extrapolate the teaching of the specification to the scope of the claims because one cannot predict that contacting any type of cell that expresses the AgRM4 with the RM4 antibody would be effective in preventing the proliferation of cells. The specification teaches that the RM4 antibody is effective in inhibiting the proliferation of colon and lung cancer cells that express the AgRM4 antigen. However, the specification also shows that viable cancer cells remain after treatment with the

antibody because a substantial increase in tumor mass is observed after the cessation of treatment with the antibody. The unpredictability of cancer treatment is well known in the art (Gura, 1997, Science 278:1041-1042). Given the known unpredictability of cancer treatment and the evidence in the specification that tumor progression rapidly commences following cessation of treatment with the RM4 antibody, one of skill in the art could not predict, and would not expect, that contacting cells that expresses the AgRM4 with the RM4 antibody would be effective in preventing the proliferation of the cells.

9. Further, if the rejection of claims 62-66 stated above were overcome, claims 62-66 would still be rejected under 35 U.S.C. 112, first paragraph, because the specification while being enabling for a method for treating hyperproliferative disorder, wherein at least a portion of the hyperproliferative cells express AgRM4 comprising administering to a subject an amount of the monoclonal antibody that is designated RM4, enabling for a method for treating hyperproliferative disorder, wherein at least a portion of the hyperproliferative cells express AgRM2 comprising administering to a subject an amount of the monoclonal antibody that is designated RM2, enabling for a method for treating hyperproliferative disorder, wherein at least a portion of the hyperproliferative cells express AgRM4 AND AGRM2 comprising administering to a subject an amount of the monoclonal antibody that is designated RM4 as well as antibody that is designated RM2, does not reasonably provide enablement for a method for treating a hyperproliferative disorder, wherein at least a portion of the hyperproliferative cells express AgRM4, comprising administering to a subject an amount of the monoclonal antibody that is designated RM2 or comprising administering to a subject the isolated human monoclonal antibody that is designated RM4 and that selectively binds to an antigen designated RM4 and the antibody denoted as RM2.

The claims are drawn to a method of treating a hyperproliferative cell disorder, wherein at least a portion of the hyperproliferative cells express AgRM4, comprising administering to a subject an amount of the isolated human monoclonal antibody that is

designated RM4 and that selectively binds to an antigen designated AgRM4, the isolated human monoclonal antibody that is designated RM2 and that selectively binds to an antigen designated AgRM2, or the antibody that is designated RM4 and the antibody that is denoted RM2.

The specification teaches the isolation of the human monoclonal antibody RM4 by pooling regional draining lymph nodes from patients with colon cancer, isolating lymphocytes from the lymph nodes and fusing the lymphocytes with RN15 cells to form hybridomas (page 43, lines 7-28), and assessing the RM4 antibody as reactive with breast, colon, gastric and lung cancer cell lines (page 45, Table 4). The specification also teaches that immunohistochemistry analysis indicates that the RM4 antibody is reactive with breast, colon, and lung tumor tissue, but is not reactive with normal tissues (page 46, Table 5). The specification also teaches that immunohistochemistry analysis indicates that the RM2 antibody is reactive with breast, lung, melanoma, pancreatic tumor tissue but is not reactive with normal tissues (page 41, Table 2). The specification also teaches that the RM4 antibody was effective in causing tumor regression in mice that were injected with a human colon cancer cell line Colo205 (page 47, lines 15 thru page 48, line 2 and Table 7) and that the combination of the RM4 antibody with the RM2 antibody showed synergistic activity in causing tumor regression in mice injected with a human lung cancer cell line Calu 1 (page 48 lines 13-23 and Figure 3). The specification also teaches that although the RM4 antibody was effective in causing tumor regression in mice in injected with Colo205, tumor progression rapidly commenced following cessation of treatment with the RM4 antibody (page 48, Table 7).

One cannot extrapolate the teaching of the specification to the enablement of the claims because one cannot predict that the invention would function as claimed in treating a subject having a hyperproliferative disorder wherein the cells are treated with an RM2 antibody and wherein the cells express the AgRM4 antigen. The specification teaches that RM4 antibody may be employed to treat lung or colon cancer that express the AgRM4 antigen. The specification does not disclose any correlation between

AgRM4 expression and AgRM2 expression. Thus, one of skill in the art could not predict that the invention would function as claimed in the treatment of hyperproliferative disorders that express the AgRM4 antigen with the RM2 antibody. Further, one cannot extrapolate the teaching of the specification to the enablement of the claims because one cannot predict that the invention would function as claimed in treating a subject having a hyperproliferative disorder wherein the cells are treated with an RM4 antibody and an RM2 antibody and wherein the cells express the AgRM4 antigen but do not express the RM2 antigen. As stated above, the specification does not disclose any correlation between AgRM4 expression and AgRM2 expression. Thus, one of skill in the art could not predict that the invention would function as claimed in the treatment of hyperproliferative disorders with RM4 antibody and the RM2 antibody, wherein the cells express the AgRM4 antigen and not the AgRM2 antigen.

10. Further, if the rejection of claims 67-83 stated above were overcome, Claims 67-83 would still be rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treating a subject having a tumor, wherein the tumor cells express AgRM4 comprising administering to a subject an amount of the monoclonal antibody that is designated RM4 effective to treat the subject, does not reasonably provide enablement for a method of treating a subject at risk of having a tumor comprising administering to the subject an amount of the human monoclonal antibody designated RM4.

The claims are drawn to a method treating a subject having or at risk of having a tumor comprising administering to the subject an amount of the antibody designated RM4 that selectively binds to an antigen designated AgRM4.

The specification teaches the isolation of the human monoclonal antibody RM4 by pooling regional draining lymph nodes from patients with colon cancer, isolating lymphocytes from the lymph nodes and fusing the lymphocytes with RN15 cells to form hybridomas (page 43, lines 7-28), and assessing the RM4 antibody as reactive with breast, colon, gastric and lung cancer cell lines (page 45, Table 4). The specification

also teaches that immunohistochemistry analysis indicates that the RM4 antibody is reactive with breast, colon, and lung tumor tissue, but is not reactive with normal tissues (page 46, Table 5). The specification also teaches that immunohistochemistry analysis indicates that the RM2 antibody is reactive with breast, lung, melanoma, pancreatic tumor tissue but is not reactive with normal tissues (page 41, Table 2). The specification also teaches that the RM4 antibody was effective in causing tumor regression in mice that were injected with a human colon cancer cell line Colo205 (page 47, lines 15 thru page 48, line 2 and Table 7) and that the combination of the RM4 antibody with the RM2 antibody showed synergistic activity in causing tumor regression in mice injected with a human lung cancer cell line Calu 1 (page 48 lines 13-23 and Figure 3). The specification also teaches that although the RM4 antibody was effective in causing tumor regression in mice in injected with Colo205, tumor progression rapidly commenced following cessation of treatment with the RM4 antibody (page 48, Table 7).

One cannot extrapolate the teaching of the specification to the enablement of the claims because one cannot predict that the invention would function as claimed in treating a subject at risk of having a tumor. The specification does not define individuals at risk of having a tumor, and there is no teaching in the specification as to when the method is to be initiated. Certainly the majority of the population of the United States has been inadvertently exposed to carcinogenic substances through exposure, for example, to second hand smoke and all of the population has been exposed to nuclear radiation from the sun. Clearly not all of these individuals or even the majority of these individuals develops a malignancy associated with the exposure and it is not clear how the claimed method would be used for these individuals. Further, although individuals have been identified who have genetic predisposition for developing cancer, it is well known in the art that not all of these individuals eventually develop the disease and that the identification of individuals with genetic risk is a developing, but not yet developed art. The undeveloped nature of this art is exemplified by Cotterchio et al, 2000, Chronic Diseases in Canada, (Electronic Version downloaded from http://www.phac-aspc.gc.ca/publicat/cdic-mcc/21-2/f_e.html) who reveal that the reference is the first

population-based family colorectal cancer registry developed within Canada and since this is a novel undertaking, there are no published reports with which to compare the data (see discussion, para 1). The reference specifically states that a high response rate is important in order to ensure that the families in the registry are representative of the population from which they are selected. However, obtaining high response rates in genetic family studies of colorectal cancer is especially challenging because of the time commitment required to complete the many phases of the data collection, issues of confidentiality and the high mortality rate among the cancer cases (see discussion, para 1). The reference specifically teaches that future research is needed to identify methods of overcoming these barriers to participation. Further the reference teaches that response bias arising from differences in characteristics between participants and non-participants is always a concern in epidemiologic studies when response rates are low, as it may lead to biased estimates of prevalence and association. Finally, the reference concludes that the study offers exciting opportunities for the study of genetic and environmental factors associated with colorectal cancer as well as providing a source for the development of chemoprevention trials, cohort studies and gene discovery projects. The reference clearly teaches that there are challenges and problems associated with the development of familial colon cancer registries which may lead to biased estimates. The reference neither teaches nor suggests how to identify which patients are at risk and should be candidates for any particular method of inhibiting malignant cell growth or when to begin these protocols. Based on the information in this reference, it is clear that the assessment of patient risk based on familial history is a developing but not a well-established art. The reference clearly suggests the lack of predictability of the art when concluding that the familial history study is useful for the ***development*** (emphasis added) of chemoprevention trials.

Further, Apantaku, Breast cancer diagnosis and screening, American Family Physician (2000, Electronic version, downloaded from http://www.healthlibrary.com/doctors2/breastcancer2.html) reveals that most women with breast cancer have no identifiable risk factors (p. 596, col 2). The reference further

teaches that women who have pre-menopausal first-degree relatives with breast cancer have a three- to fourfold increased risk of developing breast cancer than women who do not. The risk factor of their having second-degree relatives with breast cancer has not been quantified (p. 596, col 2). The reference further teaches that genetic testing is controversial and raises issues about the reliability of tests and the use made of test results (p. 597, col 1). A woman who tests negative for a particular mutation may still be at risk for developing breast cancer from a sporadic mutation or a preexisting unidentified mutation. False negative results are also possible. (P. 597, col 1). The reference then goes on to detail factors that may be involved with increased risk of breast cancer (page 597-598) and suggests that a change of diet may alter personal risk factors (p. 598, col 1). However, it must be emphasized that the language used in the reference is "may be involved", "may alter personal risk factors". The teachings here are clearly speculative at best. Finally, although one group is identified as being at increased risk, there is no teaching of how or when to begin an intervention protocol.

A review of Martin et al (Journal of the National Cancer Institute, 92:1126-1135) reveals that it is hoped that identification of genetic and environmental factors that contribute to the development of breast cancer will enhance prevention effects. The reference reviews the state of the art of breast cancer genetic components of susceptibility to breast cancer from the standpoint of both human genetics and rat models (see abstract). The reference specifically states that despite numerous studies published to date, the role of modifier genes in breast cancer susceptibility remains to be elucidated. The resolution of ambiguous results will require further carefully designed studies with sufficient sample sizes to detect small effects. The reference concludes that great strides have been made in determining the disease etiology but that further investigation is necessary and that these studies will be crucial to evaluate the importance of new genes involved in breast cancer etiology so that scientists can define better therapies and cancer prevention (p. 1132, col 1). Finally, there is no teaching of how or when to begin an intervention protocol. It is clear from the teachings of this reference that the art of identifying an individual at risk for malignant growth is a

developing but as yet undeveloped art. The reference provides no guidance on how to determine which patients are at risk or when to administer treatment in order to inhibit the malignant cell growth for which the individual is at risk.

In view of the teachings of the specification and the art of record, it is not possible to predict when or how to use the broadly claimed method with a reasonable expectation of success in the treatment of a subject at risk of having a tumor.

11. Further, if the rejections of claim 83 stated above were overcome, Claim 83 would still be rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating a subject having a tumor comprising administering to the subject an amount of the antibody RM4, wherein the tumor cells express AgRM4, and further administering the antibody RM2, wherein the tumor cells express the AgRM2 antigen, does not reasonably provide enablement for a method of treating a subject having a tumor that expresses AgRM4 comprising administering to the subject an amount of the antibody RM4 and further administering the antibody RM2.

The claim is drawn to a method treating a subject having or at risk of having a tumor comprising administering to the subject an amount of the antibody designated RM4 that selectively binds to an antigen designated AgRM4, wherein the method further comprises administering the antibody RM2.

The specification teaches the isolation of the human monoclonal antibody RM4 by pooling regional draining lymph nodes from patients with colon cancer, isolating lymphocytes from the lymph nodes and fusing the lymphocytes with RN15 cells to form hybridomas (page 43, lines 7-28), and assessing the RM4 antibody as reactive with breast, colon, gastric and lung cancer cell lines (page 45, Table 4). The specification also teaches that immunohistochemistry analysis indicates that the RM4 antibody is reactive with breast, colon, and lung tumor tissue, but is not reactive with normal tissues (page 46, Table 5). The specification also teaches that immunohistochemistry analysis indicates that the RM2 antibody is reactive with breast, lung, melanoma, pancreatic

tumor tissue but is not reactive with normal tissues (page 41, Table 2). The specification also teaches that the RM4 antibody was effective in causing tumor regression in mice that were injected with a human colon cancer cell line Colo205 (page 47, lines 15 thru page 48, line 2 and Table 7) and that the combination of the RM4 antibody with the RM2 antibody showed synergistic activity in causing tumor regression in mice injected with a human lung cancer cell line Calu 1 (page 48 lines 13-23 and Figure 3). The specification also teaches that although the RM4 antibody was effective in causing tumor regression in mice in injected with Colo205, tumor progression rapidly commenced following cessation of treatment with the RM4 antibody (page 48, Table 7).

One cannot extrapolate the teaching of the specification to the scope of the claims because one cannot predict that the invention would function as claimed in treating a subject having a tumor wherein the cells are treated with an RM4 antibody and an RM2 antibody and wherein the cells do not express the AgRM2 antigen.

12. Claims 53-66 are rejected under 35 USC 112, first paragraph, as lacking an adequate written description in the specification.

The claims are drawn to the following inventions: (i) a method of inhibiting or preventing the proliferation of a cell that expresses AgRM4 comprising contacting the cell with an amount of an isolated human monoclonal antibody that is designated RM4 and that selectively binds an antibody designated RM4 (claims 53-61), (ii) a method of treating a hyperproliferative cell disorder, wherein at least a portion of the hyperproliferative cells express AgRM4, comprising administering to a subject an amount of the isolated human monoclonal antibody that is designated RM4 and that selectively binds to an antigen designated AgRM4, the isolated human monoclonal antibody that is designated RM2 and that selectively binds to an antigen designated AgRM2, or the antibody that is designated RM4 and the antibody that is denoted RM2 (claims 62-66).

Although drawn to the DNA arts, the finding in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that

a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." Id. at 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

Although, the inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here.

Thus, the instant specification may provide an adequate written description of "a cell that expresses AgRM4" or of "a hyperproliferative disorder, wherein a portion of the hyperproliferative cells express AgRM4" per Lilly by structurally describing a representative number of species of "a cell that expresses AgRM4" or species of "a hyperproliferative disorder, wherein a portion of the hyperproliferative cells express AgRM4" or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, per Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not describe "a cell that expresses AgRM4" or of "a hyperproliferative disorder, wherein a portion of the hyperproliferative cells express AgRM4", in the methods of claims 53 61, in a manner that satisfies either the Lilly or Enzo standards. The specification does not describe "a cell that expresses AgRM4" or "a hyperproliferative disorder, wherein a portion of the hyperproliferative cells express

AgRM4 other than the description that AgRM4 antigen is expressed in breast, lung, melanoma, and pancreatic primary cancer cells (p. 46), with no expression in normal tissue, and in breast, and that the antigen is expressed in breast, lung, colon, and gastric cell lines (p. 45). Although the specification discloses the expression of the AgRM4 antigen in certain cancer tissues and cell lines, this disclosure does not provide a description of "a cell that expresses AgRM4" or of "a hyperproliferative disorder, wherein a portion of the hyperproliferative cells express AgRM4" of the claimed methods that would satisfy the standard set out in Enzo.

The specification also fails to describe the claimed "a cell that expresses AgRM4" or of "a hyperproliferative disorder, wherein a portion of the hyperproliferative cells express AgRM4", by the test set out in Lilly. The specification describes only the expression of the AgRM4 antigen in the primary tumor and cancer lines described above. Therefore, it necessarily fails to describe a "representative number" of such species. In addition, the specification also does not describe "structural features common to the members of the genus, which features constitute a substantial portion of the genus."

Thus, the specification does not provide an adequate written description of the "a cell that expresses AgRM4" or of "a hyperproliferative disorder, wherein a portion of the hyperproliferative cells express AgRM4".

13. No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Catherine M. Joyce whose telephone number is 571-272-3321. The examiner can normally be reached on Monday thru Friday, 10:15 - 6:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Catherine Joyce
Examiner
Art Unit 1642

SUSAN UNGAR, PH.D
PRIMARY EXAMINER